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CLINICAL REVIEW

Hemoglobinopathies and sleep – The road less traveled

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SUMMARY

Sickle cell disease and thalassemia are common hereditary blood disorders associated with increased systemic inflammation, tissue hypoxia, endothelial dysfunction and end-organ damage, the latter accounting for the substantial morbidity and abbreviated lifespan associated with these conditions. Sleep perturbations in general, and sleep-disordered breathing in particular are also highly prevalent conditions and the mechanisms underlying their widespread end-organ morbidities markedly and intriguingly overlap with the very same pathways implicated in the hemoglobinopathies. However, little attention has been given to date to the potential contributing role of sleep disorders to sickle cell disease manifestations. Here, we comprehensively review the pathophysiological mechanisms and clinical manifestations linking disturbed sleep and hemoglobinopathies, with special emphasis on sickle cell disease. In addition to a broad summary of the available evidence, we identify many of the research gaps that require attention and future investigation, and provide the scientific contextual setting that should enable opportunities to investigate the intertwined pathophysiological mechanisms and clinical outcomes of sleep disorders and hemoglobinopathies.

Introduction

Sickle cell disease (SCD) is a common genetic disorder with a wide range of clinical manifestation including recurrent pain attacks, acute chest syndrome, pulmonary hypertension, and upper and lower airway obstruction. Hypoxemia, especially at night, and sleep-disordered breathing (SDB) are emerging as risk factors that confer significant increases to the prevalence and severity of sickle cell disease manifestations, and even to mortality. Here, we will critically review in detail the potential epidemiological links between SCD and SDB and explore the potentially overlapping pathophysiological components of both disorders, and their potential impact on clinical phenotype and course. For the sake of completeness, we will describe the relatively scarce information currently available on the association of thalassemia, the second most common hemoglobinopathy, with sleep disorders. Based on our comprehensive literature searches toward the preparation of this review, we clearly identify a knowledge gap, as there are almost no prospective studies that have been conducted to test the impact of treating sleep disorders on the outcomes of hemoglobinopathies.

Hemoglobinopathies

Hereditary disorders of hemoglobin, also known as hemoglobinopathies, are a group of genetic disorders of hemoglobin structure. They primarily comprise two disease groups – sickle cell disease (SCD) and the thalassemias [1]. These disorders are among the most common hereditary disorders worldwide – the birth rate of people homozygous or compound heterozygotes for symptomatic globin disorders revolves around 2.4 per 1000 births, of which 1.96 have SCD and 0.44 have thalassemias [2,3].

Sickle hemoglobin (HbS) is caused by a mutation in the β-globin gene in which the 17th nucleotide is changed from thymine to adenine causing a change of the 6th amino acid from hydrophilic glutamate for the hydrophobic valine. This mutation produces a hydrophobic motif in the deoxygenated HbS tetramer that results in binding between β1 and β2 chains of two hemoglobin molecules. The hydrophobic binding between the beta chains produces an expanding polymer which fills the red blood cell, disrupting its structure and elasticity (i.e., the process of "sickling") and promotes cellular dehydration, the latter being exacerbated by physical activity and by oxidative cellular stress. The degree of hemoglobin

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Abbreviations

ACS	acute chest syndrome
AHI	apnea-hypopnea index
ANS	autonomic nervous system
CPAP	continuous positive airway pressure
hs-CRP	high-sensitivity C-reactive protein
LV	left ventricular
NFκB	nuclear factor-κappa B
NO	nitric oxide
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PFTs	pulmonary function tests
PLMS	periodic leg movements
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
REM	rapid eye movement
RBC	red blood cell
SCD	sickle cell disease
SDB	sleep disordered breathing
TRV	tricuspid regurgitation jet velocity
TST	total sleep time

deoxygenation and the intracellular HbS concentration ultimately determine the rate and the extent of HbS polymerization and sickling, the main determinant of disease severity [4]. Clinical manifestations of SCD, both acute and chronic, can be categorized according to their underlying pathophysiological process(es) – i.e., vaso-occlusive or hemolytic [5]. Vaso-occlusive complications include acute pain crises, acute chest syndrome (ACS) and osteonecrosis. Hemolytic complications, on the other hand, comprise of the spectrum of pulmonary hypertension, priapism and leg ulcers. The most common reason for emergency room visits and hospitalization in both children and adults with SCD is the occurrence of acute pain crises, which although not usually and immediately associated with end-organ damage, are severely debilitating and have been associated with increased mortality in adult SCD patients. Acute chest syndrome is the second most common cause of hospitalization in SCD patients, and is defined as a new focal lung infiltrate. The pathophysiology of ACS includes pulmonary vaso-occlusion, infection, and in some cases, fat embolism. However, the exact pathophysiology of many events remains unknown. Other less frequent complications of SCD include increased incidence of stroke, heart disease, pulmonary hypertension, renal disease and hyper-hemolysis [4].

The thalassemias are an inherited group of disorders resulting from absent or reduced synthesis of normal hemoglobin. The human hemoglobin, during all phases of development, is composed of two beta-like and two alpha-like chains of globin. During the embryonic period, the embryonic genes are active producing the embryonic hemoglobin (eta2, delta2). Between 6 and 8 wk of gestation there is a switch leading to expression of the alpha and the gamma globin genes, that produces the fetal hemoglobin – HbF (alpha-2, gamma-2). Finally, around the birth, the gamma gene is changed to the beta gene, thus producing the adult hemoglobin – HbA (alpha-2, beta-2). The type of thalassemia is defined by the defective globin gene involved – in α-thalassemia the α-globin genes are affected; and in β-thalassemia the β-globin ones. Patients with thalassemia have widely variable clinical presentations, depending on the amount of residual normal hemoglobin, ranging from nearly asymptomatic to severe anemia requiring lifelong blood transfusions with complications in multiple organ systems [1,6].

Pathophysiological considerations

SCD and SDB share some common molecular pathways that can lead to similar downstream clinical manifestations (Fig. 1). In the following several paragraphs, we will describe the similarities between these two conditions, and the available data linking those pathways between SCD and SDB.

Nocturnal hypoxemia

One of the major characteristics of SDB in general, and obstructive sleep apnea in particular, is the oscillating changes in blood gas levels. The most pronounced and well-studied phenomenon is intermittent hypoxia. Repeated cycles of hypoxia and re-oxygenation are thought to play a key role in the maladaptive responses to OSA, leading to the generation of increased oxidative stress, induction of inflammatory signaling cascades and sympathetic hyperactivation [7–13].

Hypoxia in sickle cell disease is one of the major modifiers of disease severity. At the cellular level, low oxygen levels promote HbS polymerization, which leads to red blood cell (RBC) sickling, which in turn leads to impaired blood flow through the microvasculature, thereby causing a vicious cycle of hypoxia, sickling, hemolysis, and further vaso-occlusive episodes, a set of properties that has been recently proposed as a diagnostic method to anticipate the risk of vaso-occlusive phenomena in SCD patients [14,15]. Sickling of cells under hypoxia also promotes red blood cell adhesion to endothelial cells. In addition, hypoxia results in increased reticulocyte egress from the bone marrow, and these reticulocytes exhibit greater adhesive properties to the endothelium when compared to mature erythrocytes, and thus, may further aggravate vaso-occlusion [16,17]. Tissue ischemia is the net result of all these pathological cascades, resulting in pain episodes, vaso-occlusive attacks and acute chest syndrome [18,19]. As most SCD patients are not constantly hypoxemic, the blood hypoxemia and the tissue hypoxia they experience are presumably of intermittent nature, a phenomenon that has been well documented in murine models of SCD [20]. However, as evidenced from near-infrared spectroscopy studies assessing cerebral hypoxia in SCD [21], hypoxia may be present at all times in some tissues. Consequently, the unstable nature of the magnitude of the tissue hypoxemia may be a frequent phenomenon in SCD, even when pulse oximetry appears to be in the normal range [16,22,23].

Several studies have shown that nocturnal hypoxemia is associated with higher morbidity in SCD manifesting as higher degree of anemia and lower cumulative annual average hemoglobin levels [24,25], increased pulmonary artery pressures [26], worse pulmonary function tests [25], increased left ventricular (LV) hypertrophy and LV diastolic dysfunction [27], increased incidence of priapism [28], and nocturnal enuresis [29], more frequent painful [30] and vaso-occlusive crises in general, increased incidence of CNS events [31], worse executive cognitive function [32] and even vitamin C deficiency, suggestive of reduced anti-oxidant capacity [33].

In spite of the detrimental effects of nocturnal hypoxemia described above, one should keep in mind that due to the nature of SCD, pulse oximetry, the most frequently used tool to assess nocturnal oxygen levels, may not be accurate in this population, and potentially lead to underestimates of the frequency of tissue hypoxemic events. Indeed, traditional pulse oximeters will measure carboxyhemoglobin as being oxyhemoglobin, thus overestimating the true oxygen saturation by 3–7% in patients with SCD [34,35]. Nonetheless, when detected, nocturnal oxygen desaturation should be viewed as a surrogate marker for a more severe disease, and those patients should be referred for more comprehensive evaluation. Nocturnal SpO_2 values also correlate with

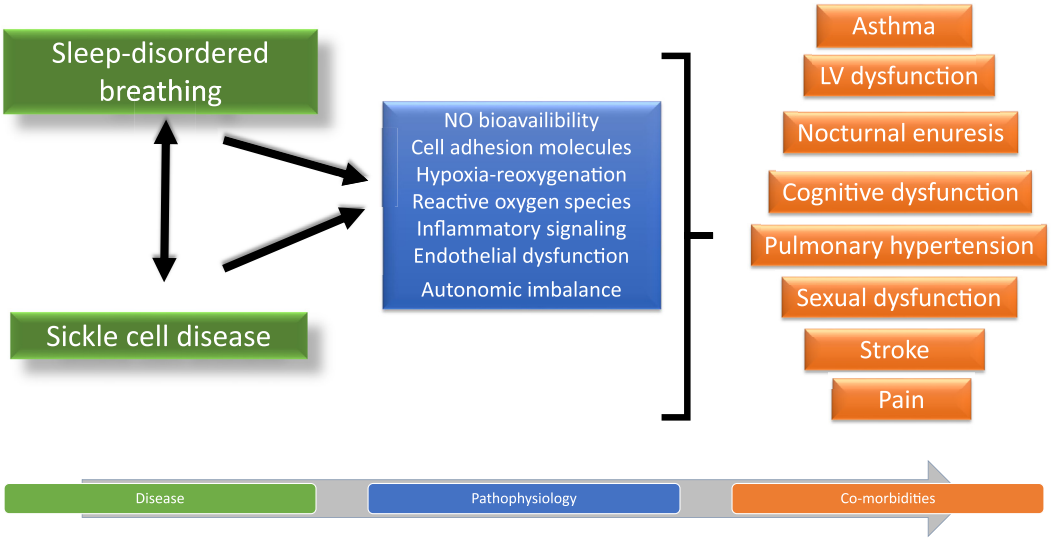

Fig. 1. Sleep disordered breathing and sickle cell disease share common pathophysiological pathways leading to substantial similarities in clinically significant morbidities.

daytime and post-exercise SpO_2 values in SCD patients [25,36], as well as with a diagnosis of OSA [37], thus emphasizing the importance of evaluating daytime oxygen saturation during any routine clinic visit, and potentially performing a standardized exercise test designed for that specific purpose.

Nitric oxide bioavailability

Nitric oxide (NO) is one of the most potent vasodilator agents. At the cellular level, decreased NO bioavailability results in endothelial dysfunction, manifested by increased adhesion of sickled RBCs to endothelial cells [19]. The mechanism for reduced NO bioavailability is through both increased NO consumption and decreased NO synthesis. Following intravascular hemolysis, RBCs release cell-free hemoglobin, which scavenges NO, along with arginase-1, which depletes arginine, the NO-synthase substrate. In addition, NO is consumed when reacting with oxygen species generated by the increased activity of NADPH oxidase and xanthine oxidase [38–40]. As NO is a key factor in SCD-associated endothelial dysfunction, it is not surprising that NO bioavailability is a major determinant of disease severity and of the frequency of vaso-occlusive events in SCD [41]. Furthermore, recent work reported abnormal endothelial function despite increased nitric oxide synthase levels and activation in red blood cells of SCD patients [42,43].

Similar to SCD, endothelial dysfunction is a well-recognized consequence of OSA in human studies and of intermittent-hypoxia in animal models. The magnitude and extent of this early stage of the pathophysiology of cardiovascular disease in OSA is an important constitutive element that modulates the time course and severity of end-organ morbidity, such as hypertension, atherosclerosis, coronary heart disease and myocardial infarction, as well as cerebrovascular disease and ischemic stroke. Altered NO synthesis has been implicated as a mechanism involved in OSA-associated endothelial dysfunction, whereby OSA induces decreased expression and activity of the eNOS gene via epigenetic modifications [44–48].

Despite the reports involving a priori similar pathways in the decreased NO bioavailability of SCD and OSA, we are unaware of any studies examining the contribution of SDB to the a priori deficient NO bioavailability in SCD. In an interesting study by Setty et al. [49], nocturnal oxygen desaturation was associated with increased adhesion of sickled RBCs and increased endothelial activation in SCD patients. Based on aforementioned considerations, it is plausible to assume that this effect is mediated by progressive and more severe decreases in NO bioavailability. We propose that it would be worthwhile to examine NO bioavailability-related pathways and endothelial function directly in SCD patients with and without SDB, and the effects of treatment on such measures.

Inflammatory cascade activation

Sickle cell disease is associated with increased systemic inflammation, owing to chronic and repeated vaso-occlusive events and cellular hypoxia. The resultant chronic low grade inflammation had been manifest as the presence of increased systemic levels of cytokines such as IL-6, TNF-α, GM-CSF, M-CSF, as well as the number of circulating leukocytes [50]. A study by Krishnan et al. also found that high-sensitivity C-reactive protein (hs-CRP) levels at steady state was a strong predictor of pain events and vaso-occlusive crises [51].

Similar to SCD, OSA is viewed as a chronic, low grade systemic inflammatory condition, with elevation in the circulating levels of inflammatory mediators, such as hs-CRP, TNFα, IL-6, and INF-γ, indicating activation of inflammatory cascades and immune dysregulation, both of which have been implicated in the deleterious consequences of OSA [52–54].

Cell adhesion molecules

Cell adhesion molecules such as ICAM-1, VCAM-1, P-selectin and E-selectin, play a significant role in the endothelial dysfunction that accompanies SCD, and contribute to the pathophysiology of vaso-occlusive crises [55–57]. Expression of these molecules on endothelial cells enhances sickle RBC and leukocyte adherence to the endothelium, and such adhesion is further enhanced by hypoxia *in vitro* [19], as well as by nocturnal hypoxemia *in vivo* [49]. Abnormal RBC and leukocyte adherence to the endothelium and circulating levels of adhesion molecules have been identified as predictors of disease severity [58,59] and mortality in SCD patients [60], making adhesion molecules potentially useful therapeutic targets in SCD.

Similarly to SCD, OSA has been also associated with enhanced synthesis and expression of cell adhesion molecules. ROS production as consequence of repeated cycles of hypoxia-re-oxygenation activates pro-inflammatory transcriptional pathways such as induction and translocation of nuclear factor-κappa B (NFκB), which up-regulates the expression of adhesion molecules, as well as

alternative inflammatory cascade signaling pathways. The role of adhesion molecules in OSA associated cardiovascular morbidities has been recently summarized by Pack and colleagues [61].

Autonomic nervous system imbalance

The maintenance of autonomic nervous system (ANS) balance between overall sympathetic and parasympathetic inputs is now a well-recognized factor in determining cardiovascular health. For example, decreased heart rate variability is a strong predictor of cardiovascular mortality [62]. In addition, ANS balance modulates the inflammatory response [63], which in turn feeds back to regulate ANS activity through vagal afferents [64]. Several studies in SCD patients have demonstrated that SCD is associated with impaired ANS balance, specifically with reduced parasympathetic activity in the basal state, and with dampening of the parasympathetic response during both physical and psychological challenges. Moreover in SCD children, increased parasympathetic withdrawal in response to a challenge is associated with a more severe clinical phenotype [65,66]. Similarly, OSA patients exhibit ANS imbalance characterized by increased sympathetic and decreased parasympathetic activities [67], and this imbalance improves after CPAP treatment [68].

Intermittent hypoxia provides a potential putative common link between ANS imbalance in SCD and SDB. Animal models of intermittent hypoxia have demonstrated loss of cells in the nucleus ambiguus, a brainstem structure from which several vagal efferent axons innervate ganglionated plexuses in cardiac atria [69]. In addition, intermittent hypoxia induces the reorganization of vagal efferent projections to cardiac ganglia with overall reduced tonic and reflexive activation patterns [70]. Consequently, intermittent hypoxia in animal models has been repeatedly associated with ANS imbalance that is characterized not only by increased sympathetic outflow but also by dampened or even markedly reduced parasympathetic responsiveness [71]. Intriguingly, even short hypoxic stimuli will result in parasympathetic withdrawal in SCD patients [72,73].

In summary, given the astounding similarities and confluence of the various pathogenetic pathways in SCD and SDB (oxygen desaturation, inflammation, adhesion molecules, NO bioavailability, ANS imbalance) (Fig. 1), and the endothelium as a common target, it appears legitimate to hypothesize that SDB exacerbates the pathophysiological pathways underlying the clinical manifestations of SCD and that such pathways may serve as common therapeutic targets. In the following sections below, we will review the evidence linking sleep and sleep-disordered breathing to organ specific manifestations of SCD.

Respiratory manifestations

Upper airway obstruction and OSA

Hypoventilation and upper airway obstruction during sleep are common precipitators of hemoglobin desaturation. Young patients with SCD are at increased risk for airway obstruction due to compensatory adenoid and tonsillar hyperplasia following splenic infarction, reactive enlargement of upper airway lymphadenoid tissues due to repeated infections, and increased extramedullary hematopoiesis due to hemolytic anemia [74]. In a recent study using MRI in SCD children, evidence suggesting the presence of a small airway size due to overgrowth of surrounding lymphoid tissues (tonsils, adenoids, deep cervical and retropharyngeal lymph nodes) was reported when compared to matched controls [75].

Despite the higher prevalence of both daytime and nighttime oxygen desaturation in patients with SCD, it has been unclear whether SCD is indeed associated with an increased risk of OSA. A recently published prospective multi-center study by Rosen et al. provides strong support to this previously enunciated assumption [27,75–83] as it demonstrated the increased incidence of OSA in children with SCD [37]. In this study, 243 children with SCD (vast majority of African descent and homozygous for HbS; mean age 10 ± 4.2 y) were prospectively and unbiasedly identified, and underwent an overnight polysomnography (PSG), while completing health and sleep questionnaires. The study evaluated mostly children with mild to moderate SCD, with children under current continuous positive airway pressure (CPAP) treatment, chronic blood transfusion, HIV positivity or chronic lung disease other than asthma being excluded. The presence of OSA, defined as an apnea-hypopnea index (AHI) $\geq$ 1/h total sleep time (TST), was present in 41% of the patients, while moderate to severe OSA (AHI $\geq$ 5/hTST) was found in 10%. In the univariate analysis, the diagnosis of OSA was associated with waking SpO_2 <96% and habitual snoring, and had a weak albeit significant association with lower FEV_1% predicted. In the multivariable analysis, only two variables were independently associated with moderate to severe OSA, namely habitual snoring (OR: 16.93; 95% CI: 4.98–57.5) and waking SpO_2 <96% (OR: 5.51; 95% CI: 1.63–18.61) [37]. The statistical model had a low positive predictive value of 32% but a high negative predictive value of 99%. The authors concluded that given the high prevalence of OSA in children with SCD, both habitual snoring and low waking SpO_2 are easily obtainable during a regular clinic visit and should be routinely screened. Another recent large retrospective study evaluated a clinic-based sample of 641 children with SCD aged 14.2 ± 5.2 y, of whom 136 (22%) were identified as having OSA by PSG [84]. In this case, the higher prevalence of OSA could reflect referral bias, such that the actual prevalence may revolve around 10% or so as suggested by Rosen et al. [37].

Multiple other studies have assessed whether indeed SCD patients have a higher incidence of OSA than the general population (Table 1). However, the vast majority of such studies consisted of either small or retrospective studies, or were biased due to inclusion of patients being referred for PSG. Nonetheless, the cumulative impression generated from the overall findings of these studies is clearly conducive to infer that the true prevalence of OSA in children with SCD is significantly higher than the estimate prevalence of 2–4% traditionally quoted for the general pediatric population, and most likely approaching 10% for moderate to severe OSA. The prevalence of habitual snoring or other conditions within the spectrum of SDB is certainly much higher, hovering around 20–40%. Moreover, the predictive value of snoring or other SDB-associated symptoms for presence of OSA seems very high, thus confirming the need for high clinical suspicion for occurrence of OSA in this vulnerable population.

Two additional questions remain unresolved regarding OSA and SCD:

1) *Do children with SCD and OSA have a more severe clinical phenotype? and*
2) *Does the treatment of OSA improve SCD co-morbidities?*

As discussed above, nocturnal hypoxemia has been strongly associated with increased disease severity in SCD, but OSA has not been specifically addressed. Most of the studies trying to assess sleep or the presence of OSA in patients with SCD have excluded those patients with a more severe clinical phenotype, thus making it difficult to address these issues. Bearing those limitations in mind, the available data described below still seem to suggest that the answer to both questions 1) and 2) are affirmative:

Although several smaller and older studies failed to identify any differences in SCD disease severity between OSA and no-OSA patients [78], a recent large data-based retrospective study by Tripathi et al. [85] would appear to suggest otherwise. Indeed, in their analysis of the South Carolina Medicaid registry from 1996 to 2006, children

Table 1
Findings in PSG studies of patients with hemoglobinopathies.

First author & publication year (ref.)	N (total)	Control group	Age (yr)	Design	Key findings
PSG studies in sickle cell disease patients					
Samuels 1992 [77]	103 (50 control)	Age matched	1.9–16.5	Case–control	SDB in 36% of SCD, no clear definition of OSA.
Raj 2006 [74]	23 (six controls)	Matched for age, sex, ethnicity	4–16	Case–control	OSA diagnosed 10% in SCD vs. 25% in controls. SCD patients without OSA showed signs of cerebral hypoxia during wakefulness, which was exacerbated during sleep.
Souza 2007 [36]	50	N/A	10–18	Cross-sectional	In SCD adolescents without prior diagnosis of OSA, TST and REM were shorter, while awakening, stage changes and movements in sleep were higher for age. Most did not fulfill criteria for OSA.
Kaleyias 2008 [76]	29 (10 controls)	Matched for age, sex, ethnicity and AHI	6–13	Case–control	79% of SCD patients with history suggestive for SDB, had OSA. More severe nocturnal desaturation and hypercapnia compared to non-SCD OSA.
Spivey 2008 [83]	20	N/A	1–19	Retrospective	In a cohort with onetime day desaturation, all had nocturnal desaturation. 35% had OSA, 20% had asthma.
Salles 2009 [24]	85	N/A	2–19	Cross-sectional	10.6% had OSA. Higher desaturation time was associated with lower mean annual Hb.
Rogers 2010 [82]	55	N/A	2–18	Retrospective	65% of children referred for SDB evaluation were diagnosed with OSA. SpO_2 was lower in HbSS vs. HbSC. PLMS were frequent
Johnson 2010 [27]	44	N/A	4–18	Cross-sectional	33% had lower SpO_2 and 19% had higher AHI than population average. 46% had LVH, LV mass and diastolic function negatively correlated with lower SpO_2
Warrier 2010 [81]	28	N/A	N/A	Retrospective	28% of children with snoring history had OSA.
Rogers 2011 [203]	64	N/A	2–18	Cross-sectional	PLMS are common (23%) and are associated with sleep disruption and symptoms of RLS.
Goldstein 2011 [80]	64	N/A	2–14	Cross-sectional	23% had SDB and 50% of them had asthma. Cerebral blood flow was similar in SDB and non-SDB groups
Mullin 2012 [205]	45	N/A	4–18	Prospective	SDB symptoms remained stable or improved over 1-y follow-up in clinically stable SCD patients
Lehman 2012 [29]	221	N/A	4–19	Prospective	AHI $\geq$ 2 was significantly associated with presence of enuresis. Severe enuresis was associated with habitual snoring and SDB
Roizenblatt 2012 [28]	34 (16 control)	SCD patients w/o Hx of priapism	16–57	Case–control	History of priapism was associated with PLMS and oxygen desaturation
Rogers 2012 [202]	20	N/A	2–18	Cross-sectional	In SCD patients with PLMS on PSG or RLS, ankle-activity monitor is a valid screening method for PLMS. PLMS were associated with higher ferritin level post-PSG and higher CRP levels overall.
Strauss 2012 [75]	72 (36 control)	Matched for age, sex, ethnicity, weight& height	2–12	Case–control	19% of SCD had OSA. SCD had reduced upper airway size on MRI due to overgrowth of surrounding lymphoid tissue.
Hollocks 2012 [32]	10	N/A	8–16	Cross-sectional	Lower nighttime SpO_2 and higher arousal index were associated with worse executive function.
Finch 2013 [79]	13	N/A	2–16	Retrospective	Adenotonsilectomy was associated with increased SpO_2 and REM sleep and reduced AHI on post-PSG as compared to pre-PSG
Katz 2014 [84]	272 (136 control)	Matched for age, gender, genotype, Hb levels	14 ± 5	Mixed retro/prospective	22% of selected SCD children had OSA. SCD + OSA had more ACS, as compared to controls, but did not differ in overall cognitive (not including executive) function.
Mascarenhas 2014 [206]	130 (65 control)	Matched for age, sex, AHI	2–17	Retrospective case–control	SCD children with OSA had lower mean and nadir SpO_2 and higher enuresis incidence (35%), as compared to AHI-matched controls
Salles 2014 [207]	85	N/A	2–19	Retrospective	Increased abdominal and cervical circumference was associated with nocturnal hypoxia
Rosen 2014 [37]	243	N/A	4–18	Prospective	41% of unselected for symptoms patients had OSA. 10% had mod-severe OSA. Habitual snoring and waking SpO_2 < 96% were strongly associated with moderate-severe OSA.
PSG studies in β-thalassemia patients					
Tarasiuk 2003 [208]	23 (10 BTH, 10 CDA-1, 13 control)	Age matched healthy children	10 ± 7	Case–control	BTH and CDA-1 was associated with increased arousal index arising partially from increased PLMS, as compared to healthy controls.
Sritippayawan 2012 [209]	120	N/A	3–15	Cross-sectional	16% had habitual snoring, 8% had OSA. Ferritin was higher in OSA group.

AHI: apnea-hypopnea index; ACS: acute chest syndrome; BTH: β-thalassemia; CDA: congenital dyserythropoetic anemia; CRP: C-reactive protein; Hb: hemoglobin; HbSC: heterozygous for hemogloin S (sicle cell trait carrier); HbSS: homozygous for hemoglobin S (sickle cell disease); Hx: history; LVH: left ventricular hypertrophy;, LV: left ventricular; MRI: magnetic resonance imaging; OSA: obstructive sleep apnea; PLMS: periodic limb movements; PSG: polysomnography; REM: rapid eye movement; RLS: restless leg syndrome; SCD: sickle cell disease; SDB: sleep-disordered breathing; TST: total sleep time; * most studies recruited stable patients without chronic transfusion of hydroxyurea, some reported HbSC patients in their cohort, but usually in small numbers.

with SCD who underwent adenotonsillectomy (n = 256) had more baseline visits for OSA, recurrent tonsillitis and stroke, as compared to matched controls with SCD but who did not require adenotonsillectomy (n = 512). More importantly, after adenotonsillectomy, there was a significant decrease in the number of clinic visits for OSA or for cerebrovascular ischemic events, but not for vaso-occlusive pain or ACS events, suggesting that some clinical aspects or severity components of SCD may be modifiable by treatment of OSA. In a prospective study, Samuels and collaborators demonstrated improvements in hypoxemia and upper airway obstruction following adenotonsillectomy in SCD patients [77], but did not address the impact of this intervention on disease severity. More recently, a study by Finch et al. [79] examined a sample of 13 children with OSA and SCD (mean AHI − 6.3/hTST) and again reported significant improvements in AHI and nocturnal SpO_2 following adenotonsillectomy, but not in the incidence of ACS or acute pain, although the follow-up duration of less than a year might have been too short. Another retrospective study by Rogers et al. [82] showed improvements in AHI and nocturnal desaturation after adenotonsillectomy in SCD children, although most of the children still had evidence of increased AHI after surgery (4.4 ± 5.5/hTST), consistent with residual OSA.

In summary, substantial evidence exists pointing to the increased incidence of upper airway obstruction in children with SCD, but thus far, there is no compelling evidence as to whether the degree of SCD severity is modified by the concurrent presence of OSA and whether treatment of the latter beneficially impacts upon SCD co-morbidities and clinical course.

Lower airway obstruction and asthma

SCD and SDB share to a certain extent some similarities in their pulmonary co-morbidities, most notably the presence of an increased incidence of asthma. Indeed, 14–48% of the children with SCD may present with signs of obstructive lung disease, diagnosed based on clinical symptoms or metacholine bronchoprovocation test. However, most studies have been inconclusive as to whether the bronchial obstruction is reversible with the use of bronchodilators, or whether the pathophysiology of altered airway function may instead be related to volume overload [86–89]. Wheezing symptoms, obstructive changes on pulmonary function tests (PFTs), and a clinical diagnosis of asthma have all been associated with an increased risk for pain events, higher rate of hospitalization for ACS and vaso-occlusive crisis and a 2.4-fold increased risk of death, as compared to children with SCD without these findings [90–96]. Apart from obstructive changes, other pulmonary abnormalities in SCD include interstitial lung disease and restrictive lung disease [90,97,98], all of which appear to become more prevalent as patients with SCD grow older [86,92,99].

The association of asthma with SDB has also been repeatedly documented. In a recent meta-analysis [100] 23.9% of children with asthma reported symptoms of SDB, as compared to 16.7% in the general population, and further stipulated that asthma is associated with a 2-fold increase in the risk of SDB. Studies in adults are less conclusive, although there seems to be an increased incidence of SDB in adult asthma patients as well, and the presence of SDB in adult OSA patients may be associated with a more severe asthmatic clinical phenotype [101–103]. Two recent studies have also shown that treatment of SDB in children is associated with significant improvements in asthma control [104,105].

We have identified only a handful of studies describing the presence of higher prevalence of asthma in SCD children with SDB. In a cross-sectional study (n = 64), children whose parents reported a strong history of snoring were referred for overnight PSG. Asthma was present in 25% of the total group, but in 50% of the children with PSG-diagnosed SDB, compared to 17% of the non-SDB group [80]. Another small retrospective study by Spivey et al. [83] found a 20% asthma prevalence in a referral convenience sample of SCD children with nocturnal hypoxemia, but did not identify evidence of increased asthma prevalence in the sub-group of children with OSA, the latter defined by increased AHI. A recent cohort also did not find increased asthma prevalence based on parent-reported symptoms of asthma in SCD children with OSA, although the control group had a high prevalence of asthma (23%) which may indicate biased population selection [37]. Although no studies have specifically examined the prevalence of sleep-disordered breathing in SCD children with asthma, given the strong association of asthma, and more so of severe asthma with SDB [104], it is likely that children with asthma and SCD will also have increased frequency of SDB, and might be prone to manifest a more severe clinical SCD phenotype, as each of those conditions alone has been associated with higher morbidity in SCD. As suggested in the future directions section, it would be reasonable to expect that treatment of SDB in the SCD population might improve their asthma control, and therefore prospective trials in this area are needed. In addition, it should be emphasized that no studies have examined asthma in the context of SDB in adult SCD patients. As OSA increases in prevalence with age in the general population, it is plausible that is also the case in SCD patients. However the effect of SDB on asthma prevalence and severity in this age group remains unknown.

Cardiovascular morbidities

Cardiovascular complications are an important morbidity of SCD, as nearly one-fourth of all deaths of adult SCD patients are attributable to cardiac causes [106]. Reported abnormalities in adults and in children include LV systolic and diastolic dysfunction [107–111], abnormal myocardial perfusion [112–115], myocardial infarction [106,116], arrhythmias [106] and pulmonary and systemic hypertension [106,110,117–122].

Pulmonary hypertension

Pulmonary hypertension is a well-recognized co-morbidity of SCD, which is in fact more common nowadays when patients with SCD have improved survival into adulthood, thereby enabling the necessary timeframe required for this complication to develop. When defined by tricuspid regurgitation jet velocity (TRV) of 2.5 m/s or higher, the reported prevalence of pulmonary hypertension is up to 30%. However, scrutiny of right-heart catheterization studies that define pulmonary hypertension as a mean pulmonary artery pressure ≥25 mmHg suggests a much lower prevalence revolving around 6–11% [120,123–125]. The pathophysiology of pulmonary hypertension in SCD is multi-factorial, and has been associated with increased hemolysis, decreased NO bioavailability, increased expression of cell adhesion molecules, and increased activity of procoagulants all of which potentially leading to pulmonary thromboembolism, airway hyperreactivity and possibly sleep-disordered breathing [5,7–16]. The nature of pulmonary vasculopathy is however mixed, with both pulmonary arterial hypertension and also secondary to left-heart failure and diastolic dysfunction [126,127]. Pulmonary hypertension is a well-established risk factor for mortality among patients with SCD, such that even a moderate increase in TRV is associated with major reductions in survival over 3.5 y in adults with SCD [118,128,129]. Accordingly, recent guidelines published by the American Thoracic Society have recommended hydroxyurea or chronic hypertransfusion therapy for SCD patients with pulmonary hypertension [121]. Studies in children have not shown as severe increases in the mortality risk of pulmonary hypertension, although increased TRV is found in 10–20% of children with SCD and is associated with declining functional capacity [130,131].

Pulmonary hypertension can also occur in patients with SDB and similarly to SCD, patients with SDB and pulmonary hypertension have increased mortality [132–134]. Despite the involvement of similar pathophysiologic pathways including endothelial dysfunction, decreases in NO activity, chronic hypoxemia with hypoxia-inducible factor signaling activation, few data exist as to the role of SDB in the genesis or exacerbation of pulmonary hypertension in SCD. An observational multi-center study by Minniti et al. [135] examined 310 patients with SCD aged 3–20 y, and found that a higher hemolysis index and awake oxygen desaturations predicted increased TRV. Although the prevalence of reported OSA was not increased in the group with pulmonary hypertension as compared to controls in this study, both hemolysis and daytime desaturation have been linked in SCD patients to SDB and nighttime hypoxia [27,83]. To the best of our knowledge, no study has specifically examined the contribution of SDB to pulmonary hypertension in SCD patients, and such data are sorely needed. An additional area that has not been studied is whether sleep architecture and sleep quality are preserved in patients with SCD with pulmonary hypertension, an area of potential importance since it would appear that patients without SCD but with pulmonary arterial hypertension suffer from reduced sleep quality [136].

Left ventricular dysfunction

LV dysfunction is a well-recognized complication of SCD. A meta-analysis by Poludasu and colleagues has summarized the available evidence on LV dysfunction in SCD as indicated from 19 studies that included 841 SCD patients and 554 controls [137]. The major findings indicated that load-independent LV variables, such as cardiac index, LV dilatation and LV end-systolic stress index were increased in the SCD patients. Conversely, load dependent variables, such as LVEF, did not differ between the two groups. This meta-analysis excluded studies that focused on pulmonary hypertension, such that the interdependency between right ventricular dysfunction and pulmonary hypertension and LV dysfunction in SCD remains unclear. However, no relationship between LV diastolic dysfunction and pulmonary hypertension was found in children with SCD [110].

Similarly, SDB is associated with a large array of cardiovascular morbidities that a priori share some, if not most of the pathophysiological factors involved in SCD (i.e., reduced NO bioavailability, increased inflammation, oxidative stress and endothelial dysfunction). SDB has been extensively associated with endothelial dysfunction and increased risk for systemic and pulmonary hypertension in both adults and children, as well as increased prevalence of atrial fibrillation, coronary heart disease, myocardial infarction and heart failure in adults [44,138–147]. Despite the similarity of cardiovascular manifestations in both SCD and SDB, and the high prevalence of SDB in patients with SCD, the direct contribution of SDB to the cardiovascular complications of SCD has not been thoroughly studied. One of the few available studies addressing this specific issue is a well-designed observational study by Johnson and colleagues [27]. In this study, 44 children with SCD with a mean age of 10.1 y were prospectively evaluated by PSG and echocardiography, as well as sampling of blood measures. Among these patients, 46% had eccentric LV hypertrophy, and the latter was inversely correlated with asleep and awake oxygen levels in the multivariate analysis. LV diastolic dysfunction was associated with lower oxygen saturations, while pulmonary hypertension, as indicated by TRV $\geq$ 2.5 m/s in this study, was not predicted by oxygen desaturations in the multivariate analysis. Interestingly, LV mass was not associated with hemoglobin levels, suggesting that oxygen desaturation, rather than anemia, may result in altered LV structure in children with SCD. The prominent contribution of hypoxia was further demonstrated in a study of adult patients with SCD and congestive heart failure in whom nighttime hypoxia, rather than apnea or arousals, predicted hemodynamic stress [148]. Future studies will need to examine the occurrence of LV dysfunction and SDB in larger pediatric and adult cohorts, and the potential benefits of CPAP or oxygen therapy in adults, or of adenotonsillectomy and supplemental oxygen in children as far as achieving improvements in cardiac function.

Neurological complications

One of the most devastating complications of SCD is stroke, with first-stroke incidence of 1:100 patient years between 2 and 5 y of age. By the age of 20, 11% of the patients have already sustained one stroke episode, and 60% of them will suffer from recurrent events. Most cases are associated with a vasculopathy of the internal carotid and middle cerebral arteries, in which aggravating factors include hypoxemia, decreased NO bioavailability, anemia and hemolysis [4]. Following the seminal Stroke Prevention in Sickle Cell Anemia (STOP) study [149], transcranial Doppler has become a standard tool to evaluate increased cerebral blood flow velocity, as a surrogate marker for the risk of stroke and a guide for transfusion therapy. Nocturnal hypoxemia in particular has been associated with an increased risk of stroke in SCD patients [31]. In addition, frank OSA diagnosis has been associated with increased risk for stroke, with risk reductions occurring following adenotonsillectomy [85].

Patients with SCD are also at risk for decreased IQ, partly due to the increased incidence of stroke, but even in children without stroke there are signs of impaired cognitive function as early as infancy and preschool years, suggesting the presence of microvascular damage to critical and vulnerable CNS regions [150]. Nighttime hypoxemia and increased arousals have been also associated with worse executive function [32,151].

An interesting association between executive dysfunction and SDB can be inferred from studies on cerebral blood flow in children with SDB – a study by Hill et al. [152] found that in healthy children with mild SDB (AHI < 5/hTST), increased cerebral blood flow velocities were strongly correlated with decreased executive function as compared to healthy controls. The marked overlap between the presence of endothelial dysfunction and cognitive deficits in children with SDB is not only striking but further suggests that altered endothelial function may adversely affect the survival of neurons in highly susceptible regions such as the frontal cortex [153,154]. Similarly, Hogan et al. [151] found that the presence of decreased IQ in adolescents with SCD but without clinical stroke (even though many had silent infarcts on MRI) was strongly correlated with both daytime SpO_2 and cerebral blood flow velocity. SpO_2 was the main mediator of the negative effect on the IQ, suggesting that increased blood flow effect on cognition is a function of hypoxemia or microvascular changes. Another interesting prospective study by Katz et al. [84] compared the cognitive function between of SCD children with and without OSA. The study did not identify any differences between the groups in terms of language functioning, academic skills, processing speed and visual-motor ability, even though the children with more severe OSA performed worse in those domains as compared to those with mild OSA. A possible explanation to the absence of obvious differences in this study may be that the authors did not specifically assess executive function domains, such as problem solving, working memory and planning, which are known to be impaired in otherwise healthy children with OSA [155]. In summary, there is evidence to support to concept that SDB may account to some degree for the adverse neurocognitive outcomes seen among SCD patients, both as an increased risk of stroke and an increased risk of cognitive impairments. However, these issues remain largely unresolved, and more specifically as to the potential benefit of therapeutic interventions for SDB in these SCD-related outcomes.

Urological complications

SCD is commonly associated with several urological abnormalities, the major ones being priapism (a medical emergency), nocturnal enuresis and erectile dysfunction [4]. Those complications result from several pathophysiological processes in SCD, such as chronic hemolysis, endothelial dysfunction and acute vaso-occlusive events.

Priapism

Priapism is a prolonged and unwanted penile erection lasting more than 4 h. The most common type of priapism in children is ischemic priapism, a medical emergency. The most common cause of priapism in children is SCD [156]. Under normal conditions, relaxation of cavernous smooth muscle cells generates normal penile erection and their contraction leads to the termination of the erection. Paradoxically, both SCD-associated hemolysis and hypoxemia decrease the biological activity of NO, the main vasodilatatory molecule. However, the decreased NO bioavailability leads also to down-regulation of phosphodiesterase-V and up-regulation of cyclic GMP, which in turn prolong arterial and trabecular smooth muscle relaxation, leading to arterial dilatation, venous constriction and finally, prolonged penile erection [5]. Despite the above mentioned association of priapism with hypoxemia, and the fact that priapism occurs mainly at night in SCD, these associations have not received major attention until recently. In a case–control study by Roizenblatt and colleagues [28], 34 adults with SCD were evaluated with a PSG for the presence of sleep disorder and were also assessed for penile rigidity during sleep. Of the 34 patients, 18 patients had a positive history of priapism in the preceding year, while 16 were matched controls, with all subjects being non-obese and without evidence of severe SCD co-morbidities. The main finding of this observational study was that patients with a positive history of priapism had disrupted sleep, i.e., more arousals and periodic leg movements (PLMS), and more severe SDB, as manifested by higher AHI, and higher oxygen desaturation index (ODI). The ODI was positively correlated with a history of priapism in a model adjusted for rapid eye movement (REM) sleep and presence of lung involvement (~50% of the subjects in each group). The time of penile rigidity as a percent of TST did not differ between the groups; however, the priapism group had more penile rigidity associated with respiratory events. Not surprisingly, penile rigidity time as % of TST was most strongly associated with a history of priapism in the regression analysis. The authors concluded that nighttime hypoxia may be associated with priapism in patients with SCD, even if causal inferences are not possible due to the study design.

Nocturnal enuresis

Nocturnal enuresis is a common and challenging problem in both children and adults with SCD. Compared to 1–15% of the general population, as much as 20–69% of children and 9% of young adults with SCD suffer from nocturnal enuresis. Despite the high prevalence of enuresis in SCD patients, the etiology and pathophysiology of this condition are not well understood. Nocturnal enuresis contributes to decreased health-related quality of life in patients with SCD, and results in lower self-esteem and even social isolation. Some presumed and co-existing etiologies include hyposthenuria with consequent nocturnal polyuria, nocturnal bladder hyperactivity and decreased capacity, increased arousal threshold, and sleep disordered breathing [157–161]. In a recent study from Turkey, nocturnal enuresis was also found to be prevalent in patients with thalassemia major [162].

Several studies have demonstrated a strong relationship between nocturnal enuresis and symptoms of SDB, specifically for nasal congestion, mouth breathing and snoring [163–168]. As early as nineteenth century, adenotonsillectomy was cited as curative therapy for nocturnal enuresis [169], and the cumulative evidence to date supports a beneficial role of surgical removal of adenoids and tonsils in the amelioration or resolution of nocturnal enuresis, at least in the pediatric population [170–174].

Similar to SCD patients, enuresis is highly prevalent in patients with SDB, and several studies have linked the presence of enuresis to the underlying presence of SDB in SCD patients. In one such cross-sectional study, SDB symptoms as measured by self-report of parents of children with SCD were significantly associated with enuresis, as were other disturbances in sleep quality, such as parasomnias and reduced total sleep time [175]. Although not specifically designed for this purpose, the aforementioned study by Rosen et al. corroborated those findings, and reported a higher prevalence of enuresis in SCD children with moderate-severe OSA – 56% as compared to 27% in controls [37]. In their multi-center study, Lehmann et al. [29] prospectively evaluated the association of enuresis and SDB. In this study, 221 children with SCD with HbSS or HbSβ were evaluated by PSG and questioned about nocturnal enuresis. Enuresis was common (38.9%), and as anticipated enuresis was more likely to be present in younger children. Two-thirds of patients with enuresis had severe enuretic symptoms, defined as ≥3 episodes per week in the last month. After adjusting for age and gender, an obstructive AHI ≥ 2/hTST was significantly associated with the presence of enuresis. Severe enuresis was associated with habitual snoring with or without SDB, and with SDB alone in a dose-dependent manner (Table 2). In summary, enuresis is more common in SCD children with SDB, and a child with SCD suffering from enuresis would likely benefit from a clinical evaluation by a pediatric sleep specialist.

Erectile dysfunction

Erectile dysfunction is defined as the inability to achieve or sustain a penile erection that is sufficient for intercourse [176]. Erectile dysfunction is common in patients with OSA with as much as 50% of male OSA patients reporting some degree of sexual dysfunction. As discussed earlier, OSA is tightly associated with increased cardiovascular risk [145], and erectile dysfunction has been similarly proposed as a phenotypic marker of cardiovascular disease [177–182]. A recent review by Hoyos and colleagues in this journal has summarized the available data on erectile dysfunction in the OSA patient population, and proposed that endothelial dysfunction, an early component of cardiovascular disease, may underlie the pathophysiologic link between OSA and erectile dysfunction [183]. Indeed, in a study from our laboratory in a murine model, we demonstrated that the reduced bioavailability of NO accounted for substantial components of the erectile dysfunciton reported in OSA [184].

In SCD patients who suffer from recurrent episodes of priapism, erectile dysfunction is not uncommon [185], and the mechanism of priapism in SCD correlates with endothelial dysfunction and NO bioavailability as discussed above [186–189].

Table 2
Habitual snoring and SDB as risk factors for severe enuresis in children with SCD.

	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Habitual snoring 3+ nights/wk	1.79 (1.04, 3.11)	1.83 (1.02, 3.29)
SDB without habitual snoring	2.55 (1.40, 4.65)	2.07 (1.09, 3.92)
SDB with habitual snoring	3.93 (1.94, 7.95)	3.23 (1.53, 6.81)

[a] Adjusted for age and gender. Adapted from [29].

We are unaware of any study that has examined the contributing effect of SDB to the erectile dysfunction occurring in SCD, although clearly such relation is plausible.

Pain, sickle cell disease and sleep quality

SCD is characterized by recurrent painful episodes, such that issues pertaining to chronic pain and its management have received substantial attention. Approximately 70% of patients with SCD suffer from frequent and recurrent bouts of vaso-occlusive pain, approaching 10–13 times a year during childhood and adolescence [190,191]. Accordingly, SCD patients are expected to suffer from sleep disturbances, as it is well established that sleep is disrupted in individuals who suffer from chronic pain in general. A recent review [192] summarized the available information on sleep in the context of pediatric patients with chronic pain, and readers are encouraged to refer to this summary.

Several studies have examined the relationship of pain in SCD and sleep quality. For example, a study of 39 children and 27 adolescents evaluated sleep quality through Pittsburgh sleep quality index (PSQI) and were asked about their pain episode history. Two-thirds of the participants reported experiencing pain in the preceding month, 91.2% had some degree of sleep disturbance, while 18.2% required sleeping medications. In this study, there was a non-statistically significant trend towards higher PSQI score with increasing pain severity, but not with pain frequency [193]. Two other studies showed that SCD was associated with increased frequency and severity of sleep disturbances in middle-school children and adolescents that resembled the patterns reported for other chronic pain syndromes (e.g., juvenile idiopathic arthritic and headache), with one notable exception – SCD was associated with a much higher prevalence of sleep-disordered breathing [194,195]. In adults with SCD, sleep disturbances are also highly prevalent (70%) and are associated with depression, older age, more days of pain and more acute pain events [196]. There is also evidence that pain and sleep quality have bi-directional effects, at least in children with SCD. Studies by Valrie and collaborators have demonstrated that pain levels are negatively associated with sleep quality. Interestingly, higher pain report during the day predicts poor sleep quality during that night, which in turn predicts higher pain intensity the following day. Negative mood might play a role in this bi-directional interaction between pain and sleep quality [197–199]. We should also remark that recent experimental evidence suggests that SDB may reduce the pain threshold thereby potentially increasing the frequency and severity of pain episodes in patients with SCD [200,201].

Is there a specific sleep disturbance more common in SCD patients? Children with SCD report difficulty falling asleep, frequent nighttime awakenings and increased daytime sleepiness, as well as symptoms of SDB, as compared to healthy controls [175,198,199]. Another study from Brazil [36] evaluated PSG in adolescents with stable SCD, and found similarly increased awakenings and movements in sleep and shorter REM sleep after adjusting for age. A recent small retrospective study also demonstrated increases in REM sleep in SCD children following adenotonsillectomy [79], but these results will require confirmation in larger prospective studies. In a number of studies by Rogers and colleagues, an increased prevalence (up to 23%) of PLMS and restless leg syndrome were noted in children with SCD, and were associated with sleep disruption [82,202,203]. Interestingly, those studies did not find a correlation between the presence of PLMS and the degree of anemia, contrary to the reports involving non-SCD pediatric patients [204]. It is possible that the absence of any relationship between PLMS and iron stores may be due to the small sample size of these studies or potentially reflect the increased ferritin levels in children with SCD due to their chronic inflammatory status.

Conclusion

In summary, there is sufficient evidence to suggest that the chronic pain of SCD, both in children and in adults, is associated with poor self-reported sleep quality. Objective measures of sleep architecture show reduced REM sleep time and increased arousals. Sleep is disturbed in patients with SCD, not only due to SDB, but potentially due to other factors such as PLMS or sleep-maintenance insomnia. This area warrants further research to elucidate the mechanisms of disrupted sleep in this patient population and to evaluate whether therapeutic interventions aimed at improving sleep quality will translate into meaningful reductions in pain frequency and severity, and improved quality of life.

Practice points

- Sleep-disordered breathing is more prevalent in patients with SCD.
- SCD and SDB share common pathophysiological pathways, most notably recurrent episodes of hypoxia-reoxygenation, decreased nitric oxide bioavailability, endothelial dysfunction, chronically increased pro-inflammatory signaling pathways, autonomic nervous system imbalance and increased generation of reactive oxygen species.
- SCD and SDB share common end-organ manifestations such as pulmonary hypertension, asthma, LV dysfunction, cognitive dysfunction and nocturnal enuresis.
- Treatment of SDB may improve SCD disease severity, but more conclusive evidence is needed.

Research agenda

Future studies will need to address the following questions:

- Does SDB contribute to the cognitive impairment and stroke risk of SCD patients and is this effect preventable by treatment of SDB?
- Is treatment of SDB associated with improved SCD disease outcomes?
- Will treatment of SDB lead to better asthma control and reduced lung function deterioration in SCD children?
- Similarly to the general population, is the prevalence of SDB increased with age in SCD patients, and if so, is it an additional under-recognized cardiopulmonary risk factor in this population?
- Does ANS instability resulting from SDB play a role in the pathophysiology of SCD?
- Is thalassemia associated with an increased incidence of SDB, and if so, does the presence of SDB promote a more severe clinical phenotype?
- Is sleep architecture disruption in SCD patients associated with SDB?
- Can treatment of sleep fragmentation and unrefreshing sleep in SCD lead to improved quality of life and reduced pain frequency and severity?
- Are there biomarkers that can predict more severe SCD phenotype or the presence of SDB in SCD patients?

Conflict of interest

The authors do not have any conflicts of interest to disclose.

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References

[1] Steinberg MH, Forget BG, Higgs DR. Disorders of hemoglobin: genetics, pathophysiology, and clinical management. Cambridge, GBR: Cambridge University Press; 2009.
[2] Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med 2005;353(11):1135–46.
[3] Modell B. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008;2008(6):480–7.
*[4] Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376(9757):2018–31.
[5] Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 2007;21(1):37–47.
*[6] Martin A, Thompson AA. Thalassemias. Pediatr Clin N Am 2013;60(6):1383–91.
[7] Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005;112(17):2660–7.
*[8] Almendros I, Wang Y, Gozal D. The polymorphic and contradictory aspects of intermittent hypoxia. Am J Physiol Lung Cell Mol Physiol 2014 Jul 15;307(2):L129–40. http://dx.doi.org/10.1152/ajplung.00089.2014. Epub 2014 May 16. Review. PubMed PMID: 24838748; PubMed Central PMCID: PMC4101794.
[9] Makarenko VV, Usatyuk PV, Yuan G, Lee MM, Nanduri J, Natarajan V, et al. Intermittent hypoxia-induced endothelial barrier dysfunction requires ROS-dependent MAP kinase activation. Am J Physiol Cell Physiol 2014;306(8):C745–52.
[10] Zhang SX, Wang Y, Gozal D. Pathological consequences of intermittent hypoxia in the central nervous system. Compr Physiol 2012;2(3):1767–77.
[11] Dumitrascu R, Heitmann J, Seeger W, Weissmann N, Schulz R. Obstructive sleep apnea, oxidative stress and cardiovascular disease: lessons from animal studies. Oxidative Med Cell Longev 2013;2013:234631.
[12] Jelic S, Le Jemtel TH. Inflammation, oxidative stress, and the vascular endothelium in obstructive sleep apnea. Trends Cardiovasc Med 2008;18(7):253–60.
[13] Hakim F, Gozal D, Kheirandish-Gozal L. Sympathetic and catecholaminergic alterations in sleep apnea with particular emphasis on children. Front Neurol 2012;3:7.
[14] Higgins JM, Eddington DT, Bhatia SN, Mahadevan L. Sickle cell vaso-occlusion and rescue in a microfluidic device. Proc Natl Acad Sci U. S. A 2007;104(51):20496–500.
*[15] Wood DK, Soriano A, Mahadevan L, Higgins JM, Bhatia SN. A biophysical indicator of vaso-occlusive risk in sickle cell disease. Sci Transl Med 2012;4(123):123ra26.
*[16] Caboot JB, Allen JL. Hypoxemia in sickle cell disease: significance and management. Paediatr Respir Rev 2014;15(1):17–23.
[17] Embury SH, Garcia JF, Mohandas N, Pennathur-Das R, Clark MR. Effects of oxygen inhalation on endogenous erythropoietin kinetics, erythropoiesis, and properties of blood cells in sickle-cell anemia. N Engl J Med 1984;311(5):291–5.
[18] Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med 2008;359(21):2254–65.
*[19] Gutsaeva DR, Montero-Huerta P, Parkerson JB, Yerigenahally SD, Ikuta T, Head CA. Molecular mechanisms underlying synergistic adhesion of sickle red blood cells by hypoxia and low nitric oxide bioavailability. Blood 2014;123(12):1917–26.
[20] Osarogiagbon UR, Choong S, Belcher JD, Vercellotti GM, Paller MS, Hebbel RP. Reperfusion injury pathophysiology in sickle transgenic mice. Blood 2000;96(1):314–20.
[21] Nahavandi M, Nichols JP, Hassan M, Gandjbakhche A, Kato GJ. Near-infrared spectra absorbance of blood from sickle cell patients and normal individuals. Hematology 2009;14(1):46–8.
[22] Pianosi P, Charge TD, Esseltine DW, Coates AL. Pulse oximetry in sickle cell disease. Arch Dis Child 1993;68(6):735–8.
[23] Trudel M, De Paepe ME, Chretien N, Saadane N, Jacmain J, Sorette M, et al. Sickle cell disease of transgenic SAD mice. Blood 1994;84(9):3189–97.
[24] Salles C, Ramos RTT, Daltro C, Barral A, Marinho JM, Matos MA. Prevalência da apneia obstrutiva do sono em crianças e adolescentes portadores da anemia falciforme. J Bras Pneumol 2009;35(11):1075–83.
[25] Halphen I, Elie C, Brousse V, Le Bourgeois M, Allali S, Bonnet D, et al. Severe nocturnal and postexercise hypoxia in children and adolescents with sickle cell disease. PloS One 2014;9(5):e97462.
[26] Pashankar FD, Carbonella J, Bazzy-Asaad A, Friedman A. Longitudinal follow up of elevated pulmonary artery pressures in children with sickle cell disease. Br J Haematol 2009;144(5):736–41.
[27] Johnson MC, Kirkham FJ, Redline S, Rosen CL, Yan Y, Roberts I, et al. Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation. Blood 2010;116(1):16–21.
[28] Roizenblatt M, Figueiredo MS, Cancado RD, Pollack-Filho F, de Almeida Santos Arruda MM, Vicari P, et al. Priapism is associated with sleep hypoxemia in sickle cell disease. J Urol 2012;188(4):1245–51.
[29] Lehmann GC, Bell TR, Kirkham FJ, Gavlak JC, Ferguson TF, Strunk RC, et al. Enuresis associated with sleep disordered breathing in children with sickle cell anemia. J Urol 2012;188(4 Suppl.):1572–6.
[30] Hargrave DR, Wade A, Evans JP, Hewes DK, Kirkham FJ. Nocturnal oxygen saturation and painful sickle cell crises in children. Blood 2003;101(3):846–8.
*[31] Kirkham FJ, Hewes DKM, Prengler M, Wade A, Lane R, Evans JPM. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet 2001;357(9269):1656–9.
[32] Hollocks MJ, Kok TB, Kirkham FJ, Gavlak J, Inusa BP, DeBaun MR, et al. Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. J Int Neuropsychological Soc JINS 2012;18(1):168–73.
[33] Cox SE, L'Esperance V, Makani J, Soka D, Hill CM, Kirkham FJ. Nocturnal haemoglobin oxygen saturation variability is associated with vitamin C deficiency in Tanzanian children with sickle cell anaemia. Acta Paediatr 2011;100(4):594–7.
[34] Craft JA, Alessandrini E, Kenney LB, Klein B, Bray G, Luban NLC, et al. Comparison of oxygenation measurements in pediatric patients during sickle cell crises. J Pediatr 1994;124(1):93–5.
[35] Needleman JP, Franco ME, Varlotta L, Reber-Brodecki D, Bauer N, Dampier C, et al. Mechanisms of nocturnal oxyhemoglobin desaturation in children and adolescents with sickle cell disease. Pediatr Pulmonol 1999;28(6):418–22.
[36] Souza LC, Viegas CA. Quality of sleep and pulmonary function in clinically stable adolescents with sickle cell anemia. J Bras Pneumol 2007;33(3):275–81. publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia.
[37] Rosen CL, Debaun MR, Strunk RC, Redline S, Seicean S, Craven DI, Gavlak JC, Wilkey O, Inusa B, Roberts I, Goodpaster RL, Malow B, Rodeghier M, Kirkham FJ. Obstructive sleep apnea and sickle cell anemia. Pediatrics 2014 Aug;134(2):273–81. http://dx.doi.org/10.1542/peds.2013-4223. Epub 2014 Jul 14. PubMed PMID: 25022740; PubMed Central PMCID: PMC4187233.
[38] Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine, and new research directions. Am J Hematol 2009;84(9):618–25.
[39] Kato GJ. No NO means yes to sickle red cell adhesion. Blood 2014;123(12):1780–2.
[40] Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon 3rd RO, Schechter AN, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med 2002;8(12):1383–9.
[41] Morris CR, Kuypers FA, Larkin S, Vichinsky EP, Styles LA. Patterns of arginine and nitric oxide in patients with sickle cell disease with vaso-occlusive crisis and acute chest syndrome. J Pediatr Hematol Oncol 2000;22(6):515–20.
[42] Grau M, Mozar A, Charlot K, Lamarre Y, Weyel L, Suhr F, Collins B, Jumet S, Hardy-Dessources MD, Romana M, Lemonne N, Etienne-Julan M, Antoine-Jonville S, Bloch W, Connes P. High red blood cell nitric oxide synthase activation is not associated with improved vascular function and red blood cell deformability in sickle cell anaemia. Br J Haematol 2014 Oct 15. http://dx.doi.org/10.1111/bjh.13185 [Epub ahead of print] PubMed PMID: 25316332.
[43] Mozar A, Grau M, Lamarre Y, Weyel L, Suhr F, Collins B, Hardy-Dessources MD, Romana M, Lemonne N, Etienne-Julan M, Bloch W, Connes P. Red blood cell nitric oxide synthase activation is increased in patients with sickle cell hemoglobin C disease. Am J Hematol 2014 Nov 7. http://dx.doi.org/10.1002/ajh.23894 [Epub ahead of print] PubMed PMID: 25379969.
*[44] Kheirandish-Gozal L, Khalyfa A, Gozal D, Bhattacharjee R, Wang Y. Endothelial dysfunction in children with obstructive sleep apnea is associated with epigenetic changes in the eNOS gene. Chest 2013;143(4):971–7.
[45] Kheirandish-Gozal L, Wang Y, Duggan RC, Harshan Vardhan S, Tan HL, Molero Ramirez H, et al. Nitric oxide production by monocytes in children with OSA and endothelial dysfunction. Clin Sci 2014;127(5):323–30.
[46] Chatsuriyawong S, Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Khalyfa AA, Wang Y, et al. Polymorphisms in nitric oxide synthase and

* The most important references are denoted by an asterisk.

endothelin genes among children with obstructive sleep apnea. BMC Med Genomics 2013;6:29.
[47] Ip MSM, Lam B, Chan LY, Zheng L, Tsang KWT, Fung PCW, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med 2000;162(6):2166–71.
[48] Fish JE, Yan MS, Matouk CC, St Bernard R, Ho JJ, Gavryushova A, et al. Hypoxic repression of endothelial nitric-oxide synthase transcription is coupled with eviction of promoter histones. J Biol Chem 2010;285(2):810–26.
[49] Setty BN, Stuart MJ, Dampier C, Brodecki D, Allen JL. Hypoxaemia in sickle cell disease: biomarker modulation and relevance to pathophysiology. Lancet 2003;362(9394):1450–5.
[50] Conran N, Franco-Penteado CF, Costa FF. Newer aspects of the pathophysiology of sickle cell disease vaso-occlusion. Hemoglobin 2009;33(1):1–16.
[51] Krishnan S, Setty Y, Betal SG, Vijender V, Rao K, Dampier C, et al. Increased levels of the inflammatory biomarker C-reactive protein at baseline are associated with childhood sickle cell vasocclusive crises. Br J Haematol 2010;148(5):797–804.
[52] Gozal D, Crabtree VM, Sans Capdevila O, Witcher LA, Kheirandish-Gozal L. C-reactive protein, obstructive sleep apnea, and cognitive dysfunction in school-aged children. Am J Respir Crit Care Med 2007;176(2):188–93.
[53] Kaditis AG, Gozal D, Khalyfa A, Kheirandish-Gozal L, Capdevila OS, Gourgoulianis K, et al. Variants in C-reactive protein and IL-6 genes and susceptibility to obstructive sleep apnea in children: a candidate-gene association study in European American and Southeast European populations. Sleep Med 2014;15(2):228–35.
[54] Gozal D, Serpero LD, Kheirandish-Gozal L, Capdevila OS, Khalyfa A, Tauman R. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. Sleep 2010;33(3):319–25.
[55] Telen MJ. Role of adhesion molecules and vascular endothelium in the pathogenesis of sickle cell disease. Hematol Educ Program Am Soc Hematol Am Soc Hematol Educ Program 2007:84–90.
[56] Zennadi R, Hines PC, De Castro LM, Cartron JP, Parise LV, Telen MJ. Epinephrine acts through erythroid signaling pathways to activate sickle cell adhesion to endothelium via LW-alphavbeta3 interactions. Blood 2004;104(12):3774–81.
[57] Turhan A, Weiss LA, Mohandas N, Coller BS, Frenette PS. Primary role for adherent leukocytes in sickle cell vascular occlusion: a new paradigm. Proc Natl Acad Sci U S A 2002;99(5):3047–51.
[58] Hebbel RP, Boogaerts MA, Eaton JW, Steinberg MH. Erythrocyte adherence to endothelium in sickle-cell anemia. A possible determinant of disease severity. N Engl J Med 1980;302(18):992–5.
[59] Johnson C, Telen MJ. Adhesion molecules and hydroxyurea in the pathophysiology of sickle cell disease. Haematologica 2008;93(4):481–5.
[60] Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol 2014;89(5):530–5.
[61] Pak VM, Grandner MA, Pack AI. Circulating adhesion molecules in obstructive sleep apnea and cardiovascular disease. Sleep Med Rev 2014;18(1):25–34.
[62] Kleiger RE, Stein PK, Bigger Jr JT. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 2005;10(1):88–101. the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc.
[63] Olofsson PS, Rosas-Ballina M, Levine YA, Tracey KJ. Rethinking inflammation: neural circuits in the regulation of immunity. Immunol Rev 2012;248(1):188–204.
[64] Andersson U, Tracey KJ. Reflex principles of immunological homeostasis. Annu Rev Immunol 2012;30:313–35.
*[65] Connes P, Coates TD. Autonomic nervous system dysfunction: implication in sickle cell disease. Comptes Rendus Biol 2013;336(3):142–7.
[66] Connes P. Altered autonomic nervous system function in sickle cell disease. Am J Respir Crit Care Med 2011;184(4):398–400.
[67] Mansukhani MP, Kara T, Caples SM, Somers VK. Chemoreflexes, sleep apnea, and sympathetic dysregulation. Curr Hypertens Reports 2014;16(9):476.
[68] Ito R, Hamada H, Yokoyama A, Oshima M, Katayama H, Ohnishi H, et al. Successful treatment of obstructive sleep apnea syndrome improves autonomic nervous system dysfunction. Clin Exp Hypertens 2005;27(2–3):259–67.
[69] Ai J, Epstein PN, Gozal D, Yang B, Wurster R, Cheng ZJ. Morphology and topography of nucleus ambiguus projections to cardiac ganglia in rats and mice. Neuroscience 2007;149(4):845–60.
[70] Lin M, Ai J, Li L, Huang C, Chapleau MW, Liu R, et al. Structural remodeling of nucleus ambiguus projections to cardiac ganglia following chronic intermittent hypoxia in C57BL/6J mice. J Comp Neurol 2008;509(1):103–17.
[71] Olea E, Agapito MT, Gallego-Martin T, Rocher A, Gomez-Nino A, Obeso A, et al. Intermittent hypoxia and diet-induced obesity: effects on oxidative status, sympathetic tone, plasma glucose and insulin levels, and arterial pressure. J Appl Physiol (1985) 2014;117(7):706–19.
[72] Sangkatumvong S, Khoo MC, Kato R, Detterich JA, Bush A, Keens TG, et al. Peripheral vasoconstriction and abnormal parasympathetic response to sighs and transient hypoxia in sickle cell disease. Am J Respir Crit Care Med 2011;184(4):474–81.
[73] Sangkatumvong S, Khoo MC, Coates TD. Abnormal cardiac autonomic control in sickle cell disease following transient hypoxia. In: Conference proceedings: annual international conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society annual conference, 2008; 2008. p. 1996–9.
[74] Raj AB, O'Brien LM, Bertolone SJ, Gozal D, Edmonds Jr HL. Cerebral oximetry improves detection of sickle cell patients at risk for nocturnal cerebral hypoxia. Pediatr Pulmonol 2006;41(11):1088–94.
[75] Strauss T, Sin S, Marcus CL, Mason TB, McDonough JM, Allen JL, et al. Upper airway lymphoid tissue size in children with sickle cell disease. Chest 2012;142(1):94–100.
[76] Kaleyias J, Mostofi N, Grant M, Coleman C, Luck L, Dampier C, et al. Severity of obstructive sleep apnea in children with sickle cell disease. J Pediatr Hematol Oncol 2008;30(9):659–65.
[77] Samuels MP, Stebbens VA, Davies SC, Picton-Jones E, Southall DP. Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. Archives Dis Child 1992;67(7):925–9.
[78] Brooks LJ, Koziol SM, Chiarucci KM, Berman BW. Does sleep-disordered breathing contribute to the clinical severity of sickle cell anemia? J Pediatr Hematol Oncol 1996;18(2):135–9.
[79] Finch P, Stocks RM, Smeltzer MP, Kimble A, Schoumacher R, Hankins JS. Effects of adenotonsillectomy on polysomnographic parameters in children with sickle cell disease. Pediatr Blood Cancer 2013;60(7):E26–8.
[80] Goldstein NA, Keller R, Rey K, Rao S, Weedon J, Dastgir G, et al. Sleep-disordered breathing and transcranial dopplers in sickle cell disease. Archives Otolaryngol Head Neck Surg 2011;137(12):1263–8.
[81] Warrier R, Chauhan A, Athale U. Tonsillectomy and adenoidectomy for obstructive sleep apnea in sickle cell anemia. Indian J Pediatr 2010;77(6):669–72.
[82] Rogers VE, Lewin DS, Winnie GB, Geiger-Brown J. Polysomnographic characteristics of a referred sample of children with sickle cell disease. J Clin Sleep Med 2010;6(4):374–81.
[83] Spivey JF, Uong EC, Strunk R, Boslaugh SE, DeBaun MR. Low daytime pulse oximetry reading is associated with nocturnal desaturation and obstructive sleep apnea in children with sickle cell anemia. Pediatr Blood Cancer 2008;50(2):359–62.
[84] Katz T. The prevalence rate and neurocognitive morbidity associated with obstructive sleep apnea in children with sickle cell disease. University of South Carolina; 2014.
[85] Tripathi A, Jerrell JM, Stallworth JR. Cost-effectiveness of adenotonsillectomy in reducing obstructive sleep apnea, cerebrovascular ischemia, vaso-occlusive pain, and ACS episodes in pediatric sickle cell disease. Ann Hematol 2011;90(2):145–50.
[86] Sylvester KP, Patey RA, Milligan P, Dick M, Rafferty GF, Rees D, et al. Pulmonary function abnormalities in children with sickle cell disease. Thorax 2004;59(1):67–70.
[87] Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. Thorax 2005;60(3):206–10.
[88] Wedderburn CJ, Rees D, Height S, Dick M, Rafferty GF, Lunt A, Greenough A. Airways obstruction and pulmonary capillary blood volume in children with sickle cell disease. Pediatr Pulmonol 2014 Jul;49(7):716–22. http://dx.doi.org/10.1002/ppul.22845. Epub 2013 Jul 8. PubMed PMID: 23836699.
[89] Chaudry RA, Rosenthal M, Bush A, Crowley S. Reduced forced expiratory flow but not increased exhaled nitric oxide or airway responsiveness to methacholine characterises paediatric sickle cell airway disease. Thorax 2014;69(6):580–5.
[90] Intzes S, Kalpatthi RV, Short R, Imran H. Pulmonary function abnormalities and asthma are prevalent in children with sickle cell disease and are associated with acute chest syndrome. Pediatr Hematol Oncol 2013;30(8):726–32.
[91] Glassberg JA, Chow A, Wisnivesky J, Hoffman R, Debaun MR, Richardson LD. Wheezing and asthma are independent risk factors for increased sickle cell disease morbidity. Br J Haematol 2012;159(4):472–9.
[92] Shilo NR, Lands LC. Asthma and chronic sickle cell lung disease: a dynamic relationship. Paediatr Respir Rev 2011;12(1):78–82.
[93] Blake K, Lima J. Asthma in sickle cell disease: implications for treatment. Anemia 2011;2011:740235.
[94] Strunk RC, Cohen RT, Cooper BP, Rodeghier M, Kirkham FJ, Warner JO, et al. Wheezing symptoms and parental asthma are associated with a physician diagnosis of asthma in children with sickle cell anemia. J Pediatr 2014;164(4):821–826 e1.
[95] Jacob E, Sockrider MM, Dinu M, Acosta M, Mueller BU. Respiratory symptoms and acute painful episodes in sickle cell disease. J Pediatr Oncol Nurs 2010;27(1):33–9. official journal of the Association of Pediatric Oncology Nurses.
[96] Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica 2007;92(8):1115–8.
[97] Cook J, Jefferis O, Matchere P, Mbale E, Rylance J. Sickle-cell disease in Malawian children is associated with restrictive spirometry: a cross-sectional survey. Int J Tuberc Lung Dis 2013;17(9):1235–8. the official

journal of the International Union against Tuberculosis and Lung Disease.
[98] Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 2006;173(11):1264–9.
[99] Arteta M, Campbell A, Nouraie M, Rana S, Onyekwere OC, Ensing G, et al. Abnormal pulmonary function and associated risk factors in children and adolescents with sickle cell anemia. J Pediatr Hematol Oncol 2014;36(3):185–9.
[100] Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. Sleep Med Rev. 2014 Oct;18(5):393–7. http://dx.doi.org/10.1016/j.smrv.2014.01.005. Epub 2014 Feb 7. PubMed PMID: 24629825.
[101] Teodorescu M, Consens FB, Bria WF, Coffey MJ, McMorris MS, Weatherwax KJ, et al. Correlates of daytime sleepiness in patients with asthma. Sleep Med 2006;7(8):607–13.
[102] ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26(5):812–8.
[103] Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? J Clin Sleep Med 2009;5(1):71–8.
[104] Bhattacharjee R, Choi BH, Gozal D, Mokhlesi B. Association of adenotonsillectomy with asthma outcomes in children: a longitudinal database analysis. PLoS Med 2014 Nov 4;11(11). http://dx.doi.org/10.1371/journal.pmed.1001753. e1001753. eCollection 2014 Nov. PubMed PMID: 25369282; PubMed Central PMCID: PMC4219664.
[105] Kheirandish-Gozal L, Dayyat EA, Eid NS, Morton RL, Gozal D. Obstructive sleep apnea in poorly controlled asthmatic children: effect of adenotonsillectomy. Pediatr Pulmonol 2011;46(9):913–8.
[106] Fitzhugh CD, Lauder N, Jonassaint JC, Telen MJ, Zhao X, Wright EC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. Am J Hematol 2010;85(1):36–40.
[107] Rees AH, Stefadouros MA, Strong WB, Miller MD, Gilman P, Rigby JA, et al. Left ventricular performance in children with homozygous sickle cell anaemia. Br Heart J 1978;40(6):690–6.
[108] Covitz W, Eubig C, Balfour IC, Jerath R, Alpert BS, Strong WB, et al. Exercise-induced cardiac dysfunction in sickle cell anemia. A radionuclide study. Am J Cardiol 1983;51(3):570–5.
[109] Denenberg BS, Criner G, Jones R, Spann JF. Cardiac function in sickle cell anemia. Am J Cardiol 1983;51(10):1674–8.
[110] Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 2007;49(4):472–9.
[111] Caldas MC, Meira ZA, Barbosa MM. Evaluation of 107 patients with sickle cell anemia through tissue doppler and myocardial performance index. J Am Soc Echocardiog 2008;21(10):1163–7.
[112] Almeida AG, Araújo F, Rego F, David C, Lopes MG, Ducla-Soares J. Abnormal myocardial flow reserve in sickle cell disease: a myocardial contrast echocardiography study. Echocardiography 2008;25(6):591–9.
[113] Acar P, Maunoury C, De Montalembert M, Dulac Y. Abnormalities of myocardial perfusion in sickle cell disease in childhood: a study of myocardial scintigraphy. Archives des Maladies du Coeur des Vaisseaux 2003;96(5):507–10.
[114] De Montalembert M, Maunoury C, Acar P, Brousse V, Sidi D, Lenoir G. Myocardial ischaemia in children with sickle cell disease. Archives Dis Child 2004;89(4):359–62.
[115] Raman SV, Simonetti OP, Cataland SR, Kraut EH. Myocardial ischemia and right ventricular dysfunction in adult patients with sickle cell disease. Haematologica 2006;91(10):1329–35.
[116] Martin CR, Johnson CS, Cobb C, Tatter D, Haywood LJ. Myocardial infarction in sickle cell disease. J Natl Med Assoc 1996;88(7):428–32.
[117] Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. Hum Pathol 2002;33(10):1037–43.
*[118] Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350(9):886–95.
[119] Vichinsky EP. Pulmonary hypertension in sickle cell disease. N Engl J Med 2004;350(9):857–9.
[120] Dosunmu AO, Balogun TM, Adeyeye OO, Daniel FA, Akinola RA, Onakoya JA, et al. Prevalence of pulmonary hypertension in sickle cell anaemia patients of a tertiary hospital in Nigeria. Niger Med J 2014;55(2):161–5. journal of the Nigeria Medical Association.
[121] Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med 2014;189(6):727–40.
[122] Becker AM, Goldberg JH, Henson M, Ahn C, Tong L, Baum M, et al. Blood pressure abnormalities in children with sickle cell anemia. Pediatr Blood Cancer 2014;61(3):518–22.
[123] Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365(1):44–53.
[124] Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA J Am Med Assoc 2012;307(12):1254–6.
[125] Fonseca GHH, Souza R, Salemi VMC, Jardim CVP, Gualandro SFM. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J 2012;39(1):112–8.
[126] Klings ES, Anton Bland D, Rosenman D, Princeton S, Odhiambo A, Li G, et al. Pulmonary arterial hypertension and left-sided heart disease in sickle cell disease: clinical characteristics and association with soluble adhesion molecule expression. Am J Hematol 2008;83(7):547–53.
[127] Machado RF, Gladwin MT. Pulmonary hypertension in hemolytic disorders: pulmonary vascular disease: the global perspective. Chest 2010;137(6 Suppl.):30S–8S.
[128] Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA J Am Med Assoc 2006;296(3):310–8.
*[129] Cabrita IZ, Mohammed A, Layton M, Ghorashian S, Gilmore A, Cho G, et al. The association between tricuspid regurgitation velocity and 5-year survival in a North West London population of patients with sickle cell disease in the United Kingdom. Br J Haematol 2013;162(3):400–8.
[130] Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: relevance to children. Pediatr Hematol Oncol 2007;24(3):159–70.
[131] Gordeuk VR, Minniti CP, Nouraie M, Campbell AD, Rana SR, Luchtman-Jones L, et al. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of follow up in children and adolescents with sickle cell anemia. Haematologica 2011;96(1):33–40.
[132] Dumitrascu R, Tiede H, Eckermann J, Mayer K, Reichenberger F, Ghofrani HA, et al. Sleep apnea in precapillary pulmonary hypertension. Sleep Med 2013;14(3):247–51.
[133] Sun X, Luo J, Xiao Y. Continuous positive airway pressure is associated with a decrease in pulmonary artery pressure in patients with obstructive sleep apnoea: a meta-analysis. Respirology 2014 Jul;19(5):670–4. http://dx.doi.org/10.1111/resp.12314. Epub 2014 May 9. PubMed PMID: 24810973.
[134] Minic M, Granton JT, Ryan CM. Sleep disordered breathing in group 1 pulmonary arterial hypertension. J Clin Sleep Med 2014;10(3):277–83. JCSM : official publication of the American Academy of Sleep Medicine.
[135] Minniti CP, Sable C, Campbell A, Rana S, Ensing G, Dham N, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. Haematologica 2009;94(3):340–7.
[136] Matura LA, McDonough A, Hanlon AL, Carroll DL, Riegel B. Sleep disturbance, symptoms, psychological distress, and health-related quality of life in pulmonary arterial hypertension. Eur J Cardiovasc Nurs 2014 May 27. pii: 1474515114537951. [Epub ahead of print] PubMed PMID: 24867878.
[137] Poludasu S, Ramkissoon K, Salciccioli L, Kamran H, Lazar JM. Left ventricular systolic function in sickle cell anemia: a meta-analysis. J Cardiac Fail 2013;19(5):333–41.
[138] Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172(5):613–8.
[139] Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis 2009;51(5):434–51.
[140] Chouchou F, Pichot V, Pepin JL, Tamisier R, Celle S, Maudoux D, et al. Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: the PROOF-SYNAPSE study. Eur Heart J 2013;34(28):2122–31.
[141] Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370(24):2276–85.
[142] Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circulation Cardiovasc Qual Outcomes 2012;5(5):720–8.
[143] Querejeta Roca G, Redline S, Punjabi N, Claggett B, Ballantyne CM, Solomon SD, Shah AM. Sleep apnea is associated with subclinical myocardial injury in the community. The ARIC-SHHS study. Am J Respir Crit Care Med 2013 Dec 15;188(12):1460–5. http://dx.doi.org/10.1164/rccm.201309-1572OC. PubMed PMID: 24156237; PubMed Central PMCID: PMC3917380.
[144] Bhattacharjee R, Kim J, Alotaibi WH, Kheirandish-Gozal L, Capdevila OS, Gozal D. Endothelial dysfunction in children without hypertension: potential contributions of obesity and obstructive sleep apnea. Chest 2012;141(3):682–91.
[145] Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med 2008;177(4):369–75.
[146] Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Molero-Ramirez H, Tan HL, Bandla HP. Circulating adropin concentrations in pediatric obstructive sleep apnea: potential relevance to endothelial function. J Pediatr 2013;163(4):1122–6.
[147] Kheirandish-Gozal L, Etzioni T, Bhattacharjee R, Tan HL, Samiei A, Molero Ramirez H, et al. Obstructive sleep apnea in children is associated with severity-dependent deterioration in overnight endothelial function. Sleep Med 2013;14(6):526–31.
[148] Gottlieb JD, Schwartz AR, Marshall J, Ouyang P, Kern L, Shetty V, et al. Hypoxia, not the frequency of sleep apnea, induces acute hemodynamic stress in patients with chronic heart failure. J Am Coll Cardiol 2009;54(18):1706–12.

[149] Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339(1):5–11.
[150] Wang WC, Langston JW, Steen RG, Wynn LW, Mulhern RK, Wilimas JA, et al. Abnormalities of the central nervous system in very young children with sickle cell anemia. J Pediatr 1998;132(6):994–8.
[151] Hogan AM, Pit-ten Cate IM, Vargha-Khadem F, Prengler M, Kirkham FJ. Physiological correlates of intellectual function in children with sickle cell disease: hypoxaemia, hyperaemia and brain infarction. Dev Sci 2006;9(4):379–87.
[152] Hill CM, Hogan AM, Onugha N, Harrison D, Cooper S, McGrigor VJ, et al. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics 2006;118(4):e1100–8.
[153] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11(1):1–16.
[154] Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics 2010;126(5):e1161–7.
[155] Kheirandish-Gozal L, Yoder K, Kulkarni R, Gozal D, Decety J. Preliminary functional MRI neural correlates of executive functioning and empathy in children with obstructive sleep apnea. Sleep 2014;37(3):587–92.
[156] Donaldson JF, Rees RW, Steinbrecher HA. Priapism in children: a comprehensive review and clinical guideline. J Pediatr Urol 2014;10(1):11–24.
[157] Wolf RB, Kassim AA, Goodpaster RL, DeBaun MR. Nocturnal enuresis in sickle cell disease. Expert Rev Hematol 2014;7(2):245–54.
[158] Field JJ, Austin PF, An P, Yan Y, DeBaun MR. Enuresis is a common and persistent problem among children and young adults with sickle cell anemia. Urology 2008;72(1):81–4.
[159] Figueroa TE, Benaim E, Griggs ST, Hvizdala EV. Enuresis in sickle cell disease. J Urol 1995;153(6):1987–9.
[160] Portocarrero ML, Portocarrero ML, Sobral MM, Lyra I, Lordelo P, Barroso Jr U. Prevalence of enuresis and daytime urinary incontinence in children and adolescents with sickle cell disease. J Urol 2012;187(3):1037–40.
[161] Barakat LP, Smith-Whitley K, Schulman S, Rosenberg D, Puri R, Ohene-Frempong K. Nocturnal enuresis in pediatric sickle cell disease. J Dev Behav Pediatr JDBP 2001;22(5):300–5.
[162] Ekinci O, Celik T, Unal S, Oktay G, Toros F, Ozer C. Nocturnal enuresis in sickle cell disease and thalassemia major: associated factors in a clinical sample. Int J Hematol 2013;98(4):430–6.
[163] Khaleghipour S, Masjedi M, Kelishadi R. The effect of breathing exercises on the nocturnal enuresis in the children with the sleep-disordered breathing. Iran Red Crescent Med J 2013;15(11):e8986.
[164] Sakellaropoulou AV, Hatzistilianou MN, Emporiadou MN, Aivazis VT, Goudakos J, Markou K, et al. Association between primary nocturnal enuresis and habitual snoring in children with obstructive sleep apnoea-hypopnoea syndrome. Archives Med Sci AMS 2012;8(3):521–7.
[165] Aydil U, Iseri E, Kizil Y, Bodur S, Ceylan A, Uslu S. Obstructive upper airway problems and primary enuresis nocturna relationship in pediatric patients: reciprocal study. J Otolaryngol Head Neck Surg 2008;37(2):235–9. Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale.
[166] Barone JG, Hanson C, DaJusta DG, Gioia K, England SJ, Schneider D. Nocturnal enuresis and overweight are associated with obstructive sleep apnea. Pediatrics 2009;124(1):e53–9.
[167] Alexopoulos EI, Kostadima E, Pagonari I, Zintzaras E, Gourgoulianis K, Kaditis AG. Association between primary nocturnal enuresis and habitual snoring in children. Urology 2006;68(2):406–9.
[168] Capdevila OS, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. Proc Am Thorac Soc 2008;5(2):274–82.
[169] Salmon MA. An historical account of nocturnal enuresis and its treatment. Proc R Soc Med 1975;68(7):443–5.
[170] Firoozi F, Batniji R, Aslan AR, Longhurst PA, Kogan BA. Resolution of diurnal incontinence and nocturnal enuresis after adenotonsillectomy in children. J Urol 2006;175(5):1885–8.
[171] Basha S, Bialowas C, Ende K, Szeremeta W. Effectiveness of adenotonsillectomy in the resolution of nocturnal enuresis secondary to obstructive sleep apnea. Laryngoscope 2005;115(6):1101–3.
[172] Thottam PJ, Kovacevic L, Madgy DN, Abdulhamid I. Sleep architecture parameters that predict postoperative resolution of nocturnal enuresis in children with obstructive sleep apnea. Ann Oto Rhinol Laryn 2013;122(11):690–4.
[173] Leiberman A, Stiller-Timor L, Tarasiuk A, Tal A. The effect of adenotonsillectomy on children suffering from obstructive sleep apnea syndrome (OSAS): the Negev perspective. Int J Pediatr Otorhinolaryngol 2006;70(10):1675–82.
[174] Ahmadi MS, Amirhassani S, Poorolajal J. The effect of adenotonsillectomy on pediatric nocturnal enuresis: a prospective cohort study. Iran J Otorhinolaryngol 2013;25(70):37–40.
[175] Daniel LC, Grant M, Kothare SV, Dampier C, Barakat LP. Sleep patterns in pediatric sickle cell disease. Pediatr Blood Cancer 2010;55(3):501–7.
[176] Lue TF. Erectile dysfunction. N Engl J Med 2000;342(24):1802–13.
[177] Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol 2014;65(5):968–78.
[178] Arruda-Olson AM, Olson LJ, Nehra A, Somers VK. Sleep apnea and cardiovascular disease. Implications for understanding erectile dysfunction. Herz 2003;28(4):298–303.
[179] Margel D, Cohen M, Livne PM, Pillar G. Severe, but not mild, obstructive sleep apnea syndrome is associated with erectile dysfunction. Urology 2004;63(3):545–9.
[180] Goncalves MA, Guilleminault C, Ramos E, Palha A, Paiva T. Erectile dysfunction, obstructive sleep apnea syndrome and nasal CPAP treatment. Sleep Med 2005;6(4):333–9.
[181] Budweiser S, Enderlein S, Jorres RA, Hitzl AP, Wieland WF, Pfeifer M, et al. Sleep apnea is an independent correlate of erectile and sexual dysfunction. J Sex Med 2009;6(11):3147–57.
[182] Li X, Dong Z, Wan Y, Wang Z. Sildenafil versus continuous positive airway pressure for erectile dysfunction in men with obstructive sleep apnea: a meta-analysis. Aging Male 2010;13(2):82–6. the official journal of the International Society for the Study of the Aging Male.
[183] Hoyos CM, Melehan KL, Phillips CL, Grunstein RR, Liu PY. To ED or not to ED – Is erectile dysfunction in obstructive sleep apnea related to endothelial dysfunction? Sleep Med Rev 2014 Mar 18. http://dx.doi.org/10.1016/j.smrv.2014.03.004. pii: S1087–0792(14)00025-2 [Epub ahead of print] Review. PubMed PMID: 24813467.
[184] Soukhova-O'Hare GK, Shah ZA, Lei ZM, Nozdrachev AD, Rao CV, Gozal D. Erectile dysfunction in a murine model of sleep apnea. Am J Respir Crit Care Med 2008;178(6):644–50.
[185] Gani J, Radomski SB. Management of erectile dysfunction in patients with sickle cell disease. J Sex Med 2011;8(8):2123–7. quiz 8.
[186] Oguanobi NI, Onwubere BJ, Anisiuba BC, Ike SO, Ejim EC, Ibegbulam OG. Clinical findings associated with cardiovascular autonomic dysfunction in adult sickle cell anaemia patients. Acta Cardiol 2012;67(2):169–75.
[187] Lagoda G, Sezen SF, Cabrini MR, Musicki B, Burnett AL. Molecular analysis of erection regulatory factors in sickle cell disease associated priapism in the human penis. J Urol 2013;189(2):762–8.
[188] Bivalacqua TJ, Musicki B, Hsu LL, Berkowitz DE, Champion HC, Burnett AL. Sildenafil citrate-restored eNOS and PDE5 regulation in sickle cell mouse penis prevents priapism via control of oxidative/nitrosative stress. PloS One 2013;8(7):e68028.
[189] Burnett AL, Anele UA, Trueheart IN, Strouse JJ, Casella JF. Randomized controlled trial of sildenafil for preventing recurrent ischemic priapism in sickle cell disease. Am J Med 2014;127(7):664–8.
[190] Steinberg MH. Management of sickle cell disease. N Engl J Med 1999;340(13):1021–30.
[191] Dampier C, Setty BN, Eggleston B, Brodecki D, O'Neal P, Stuart M. Vaso-occlusion in children with sickle cell disease: clinical characteristics and biologic correlates. J Pediatr Hematol Oncol 2004;26(12):785–90.
[192] Valrie CR, Bromberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. J Dev Behav Pediatr JDBP 2013;34(2):120–8.
[193] Graves JK, Jacob E. Pain, coping, and sleep in children and adolescents with sickle cell disease. J Child Adolesc Psychiatr Nurs 2014 Aug;27(3):109–20. http://dx.doi.org/10.1111/jcap.12077. Epub 2014 Jun 17. PubMed PMID: 24934076.
[194] Long AC, Krishnamurthy V, Palermo TM. Sleep disturbances in school-age children with chronic pain. J Pediatr Psychol 2008;33(3):258–68.
[195] Palermo TM, Kiska R. Subjective sleep disturbances in adolescents with chronic pain: relationship to daily functioning and quality of life. J Pain 2005;6(3):201–7. official journal of the American Pain Society.
[196] Wallen GR, Minniti CP, Krumlauf M, Eckes E, Allen D, Oguhebe A, et al. Sleep disturbance, depression and pain in adults with sickle cell disease. BMC Psychiatry 2014;14:207.
[197] Valrie CR, Gil KM, Redding-Lallinger R, Daeschner C. Daily mood as a mediator or moderator of the pain-sleep relationship in children with sickle cell disease. J Pediatr Psychol 2008;33(3):317–22.
[198] Valrie CR, Gil KM, Redding-Lallinger R, Daeschner C. Brief report: sleep in children with sickle cell disease: an analysis of daily diaries utilizing multilevel models. J Pediatr Psychol 2007;32(7):857–61.
[199] Valrie CR, Gil KM, Redding-Lallinger R, Daeschner C. The influence of pain and stress on sleep in children with sickle cell disease. Child Health Care 2007;36(4):335–53.
[200] Wu J, Li P, Wu X, Chen W. Chronic intermittent hypoxia decreases pain sensitivity and increases the expression of HIF1α and opioid receptors in experimental rats. Sleep Breath 2014:1–8.
[201] Doufas AG, Tian L, Padrez KA, Suwanprathes P, Cardell JA, Maecker HT, et al. Experimental pain and opioid Analgesia in volunteers at high risk for obstructive sleep apnea. PloS One 2013;8(1).
[202] Rogers VE, Gallagher PR, Marcus CL, Ohene-Frempong K, Traylor JT, Mason TB. Capturing PLMS and their variability in children with sickle cell disease: does ankle activity monitoring measure up to polysomnography? Sleep Med 2012;13(8):1013–20.

[203] Rogers VE, Marcus CL, Jawad AF, Smith-Whitley K, Ohene-Frempong K, Bowdre C, et al. Periodic limb movements and disrupted sleep in children with sickle cell disease. Sleep 2011;34(7):899–908.
[204] Simakajornboon N, Gozal D, Vlasic V, Mack C, Sharon D, McGinley BM. Periodic limb movements in sleep and iron status in children. Sleep 2003;26(6):735–8.
[205] Mullin JE, Cooper BP, Kirkham FJ, Rosen CL, Strunk RC, DeBaun MR, et al. Stability of polysomnography for one year and longer in children with sickle cell disease. J Clin Sleep Med 2012;8(5):535–9. JCSM : official publication of the American Academy of Sleep Medicine.
[206] Mascarenhas MI, Loureiro HC, Ferreira T, Dias A. Sleep pathology characterization in sickle cell disease: Case-control study. Pediatr Pulmonol 2014 Jul 10. http://dx.doi.org/10.1002/ppul.23074 [Epub ahead of print] PubMed PMID: 25045078.
[207] Salles C, Bispo M, Trindade-Ramos RT. Association between morphometric variables and nocturnal desaturation in sickle-cell anemia. J Pediatr (Rio J) 2014 Jul-Aug;90(4):420–5. http://dx.doi.org/10.1016/j.jped.2014.01.005. Epub 2014 Mar 28. PubMed PMID: 24680898.
[208] Tarasiuk A, Abdul-Hai A, Moser A, Freidman B, Tal A, Kapelushnik J. Sleep disruption and objective sleepiness in children with beta-thalassemia and congenital dyserythropoietic anemia. Archiv Pediatr Adolesc Med 2003;157(5):463–8.
[209] Sritippayawan S, Norasetthekul S, Nuchprayoon I, Deerojanawong J, Desudchit T, Prapphal N. Obstructive sleep apnea among children with severe beta-thalassemia. Se Asian J Trop Med 2012;43(1):152–9.